CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 64156

Trade Name Cefaclor Capsules 250mg and 500mg

Generic Name Cefaclor Capsules 250mg and 500mg

Sponsor Ranbaxy Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 64156

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 64156

APPROVAL LETTER

AADA 64-156

AUG 28 1997

Ranbaxy Laboratories Limited
U.S. Agent: Ranbaxy Pharmaceuticals Inc.
Attention: Jim Sibert
4600 Marriott Drive
Suite 100
Raleigh, NC 27612

Dear Sir:

This is in reference to your abbreviated antibiotic application dated July 7, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Cefaclor Capsules USP, 250 mg (base) and 500 mg (base).

Reference is also made to your amendments dated June 19 and 26, October 10 and 21, November 12, and December 4, 1996; February 21, March 24, May 2, and May 27, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cefaclor Capsules USP, 250 mg and 500 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ceclor® Capsules 250 mg and 500 mg, respectively, of Eli Lilly and Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gordon R Johnston for 8/28/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA 64-156
Division File
FIELD COPY
HFD-610/JPhillips
HFD-92
HFD-210/B.Poole

Endorsements:
HFD-643/R.Adams/7-
HFD-643/J.Harris
HFD-617/M.Anderso
HFD-613/A.Payne/7-
HFD-613/J.Grace/

7/29/97
7/29/97
7/30/97
8/13/97

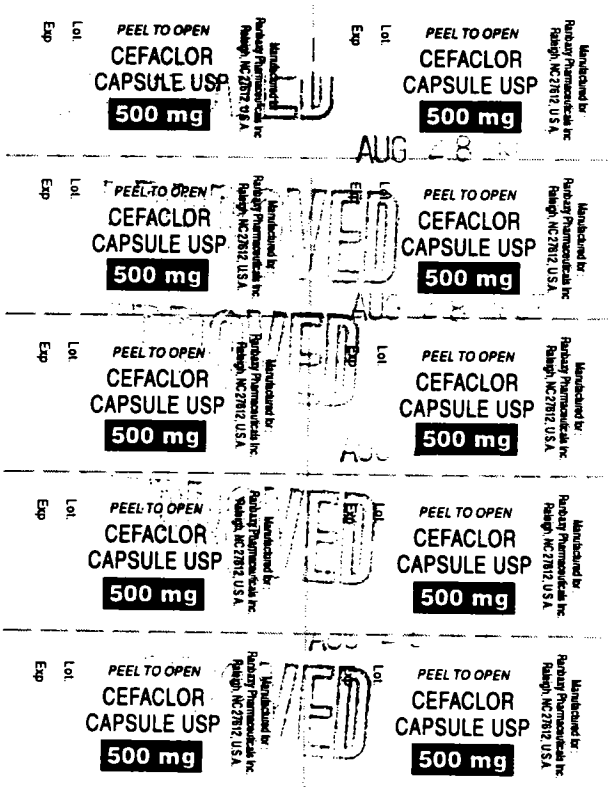
F/T by MM 7/25/97

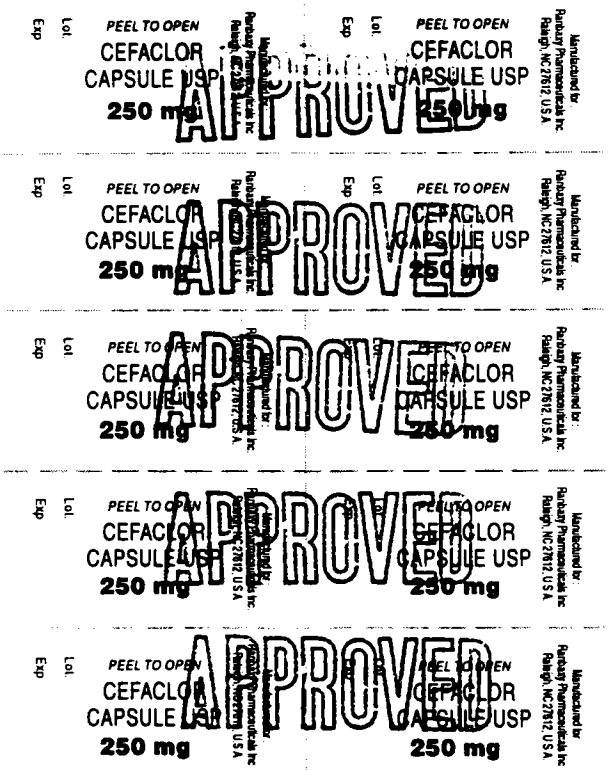
APPROVAL

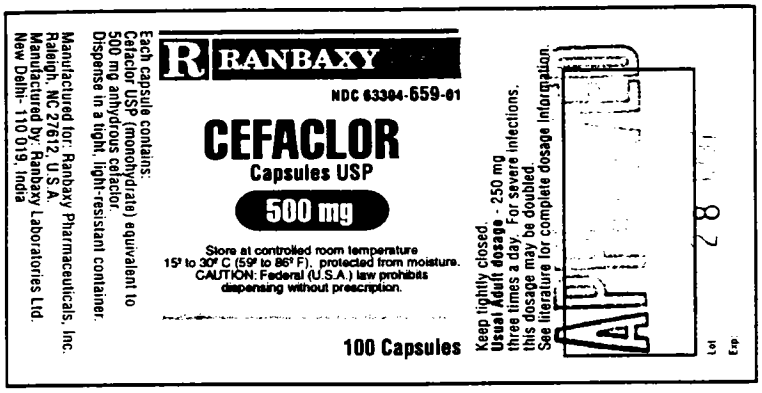
CENTER FOR DRUG EVALUATION AND RESEARCH

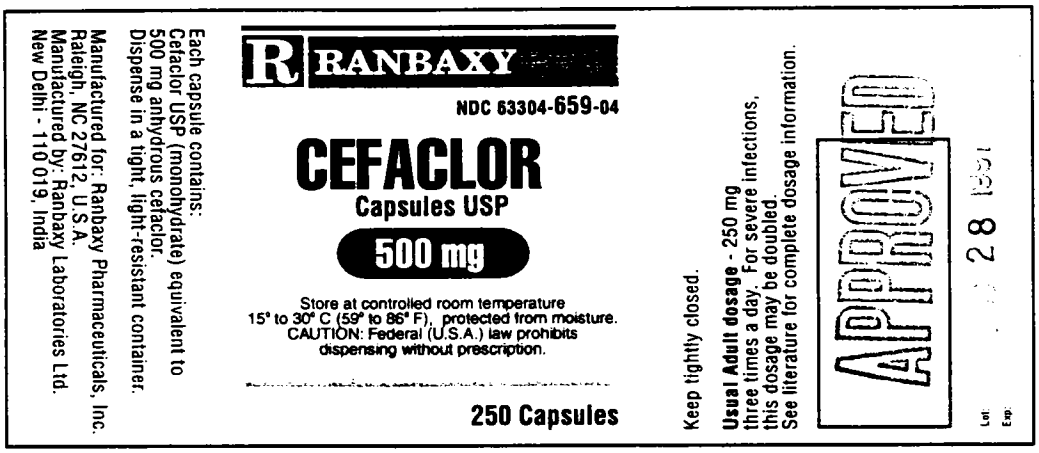
APPLICATION NUMBER 64156

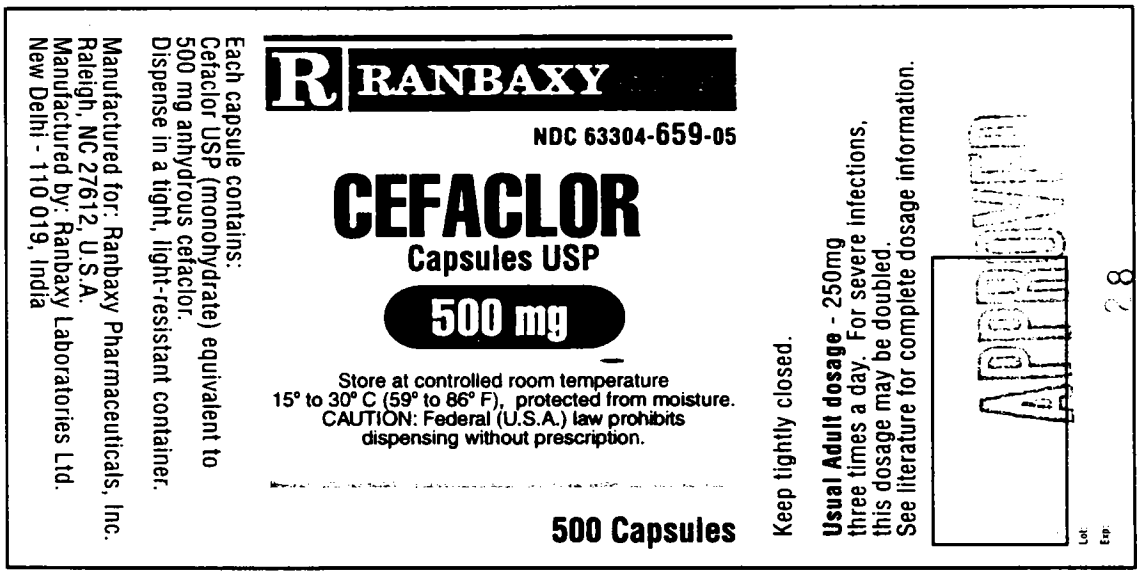
FINAL PRINTED LABELING

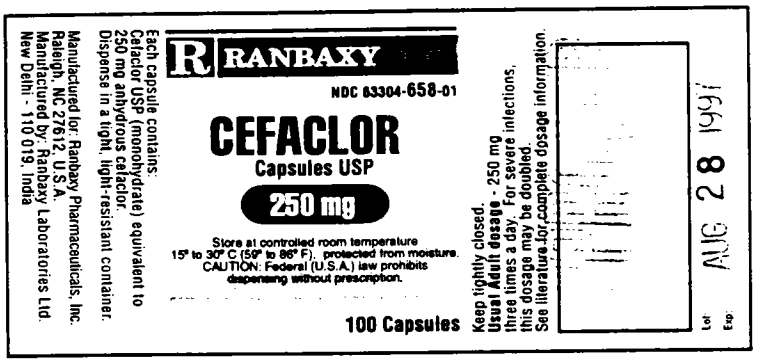

PEEL TO OPEN
CEFACLOR
CAPSULE USP
500 mg
Lot
Exp
Manufactured for
Ranbaxy Pharmaceuticals Inc
Raleigh, NC 27612, U.S.A.


PEEL TO OPEN
CEFACLOR
CAPSULE USP
250 mg
Exp
Lot
Manufactured for
Ranbaxy Pharmaceuticals Inc
Raleigh, NC 27612, U.S.A.
APPROVED


RANBAXY
NDC 63304-659-01
CEFACLOR
Capsules USP
500 mg
Store at controlled room temperature
15° to 30° C (59° to 86° F), protected from moisture.
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.
100 Capsules
Each capsule contains:
Cefaclor USP (monohydrate) equivalent to
500 mg anhydrous cefaclor.
Dispense in a tight, light-resistant container.
Manufactured for: Ranbaxy Pharmaceuticals, Inc.
Raleigh, NC 27612, U.S.A.
Manufactured by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India
Keep tightly closed.
Usual Adult dosage - 250 mg
three times a day. For severe infections,
this dosage may be doubled.
See literature for complete dosage information.
APPROVED
Lot
Exp


RANBAXY
NDC 63304-659-04
CEFACLOR
Capsules USP
500 mg
Store at controlled room temperature
15° to 30° C (59° to 86° F), protected from moisture.
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.
250 Capsules
Each capsule contains:
Cefaclor USP (monohydrate) equivalent to
500 mg anhydrous cefaclor.
Dispense in a tight, light-resistant container.
Manufactured for: Ranbaxy Pharmaceuticals, Inc.
Raleigh, NC 27612, U.S.A.
Manufactured by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India
Keep tightly closed.
Usual Adult dosage - 250 mg
three times a day. For severe infections,
this dosage may be doubled.
See literature for complete dosage information.
APPROVED
Lot
Exp


RANBAXY
NDC 63304-659-05
CEFACLOR
Capsules USP
500 mg
Store at controlled room temperature
15° to 30° C (59° to 86° F), protected from moisture.
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.
500 Capsules
Each capsule contains:
Cefaclor USP (monohydrate) equivalent to
500 mg anhydrous cefaclor.
Dispense in a tight, light-resistant container.
Manufactured for: Ranbaxy Pharmaceuticals, Inc.
Raleigh, NC 27612, U.S.A.
Manufactured by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India
Keep tightly closed.
Usual Adult dosage - 250mg
three times a day. For severe infections,
this dosage may be doubled.
See literature for complete dosage information.
APPROVED
Lot
Exp


RANBAXY
NDC 63304-658-01
CEFACLOR
Capsules USP
250 mg
Store at controlled room temperature
15° to 30° C (59° to 86° F), protected from moisture.
CAUTION: Federal (U.S.A.) law prohibits
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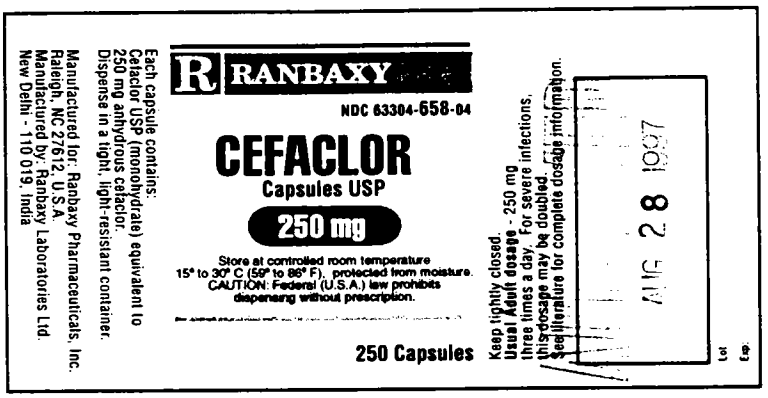
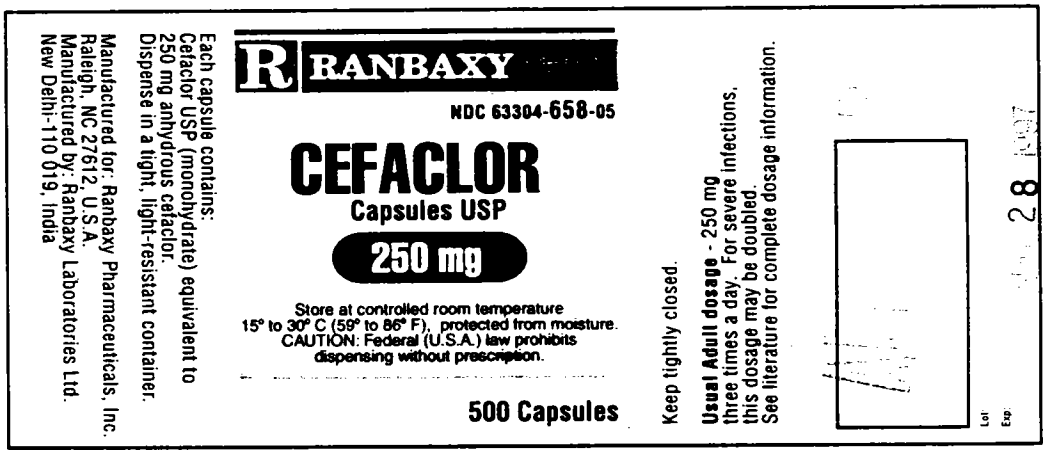
100 Capsules
Each capsule contains:
Cefaclor USP (monohydrate) equivalent to
250 mg anhydrous cefaclor.
Dispense in a tight, light-resistant container.
Manufactured for: Ranbaxy Pharmaceuticals, Inc.
Raleigh, NC 27612, U.S.A.
Manufactured by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India
Keep tightly closed.
Usual Adult dosage - 250 mg
three times a day. For severe infections,
this dosage may be doubled.
See literature for complete dosage information.
Lot
Exp
AUG 28 1997


RANBAXY
NDC 63304-658-04
CEFACLOR
Capsules USP
250 mg
Store at controlled room temperature
15° to 30° C (59° to 86° F), protected from moisture.
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.
250 Capsules
Each capsule contains:
Cefaclor USP (monohydrate) equivalent to
250 mg anhydrous cefaclor.
Dispense in a tight, light-resistant container.
Manufactured for: Ranbaxy Pharmaceuticals, Inc.
Raleigh, NC 27612, U.S.A.
Manufactured by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India
Keep tightly closed.
Usual Adult dosage - 250 mg
three times a day. For severe infections,
this dosage may be doubled.
See literature for complete dosage information.
Lot
Exp
AUG 28 1997


RANBAXY
NDC 63304-658-05
CEFACLOR
Capsules USP
250 mg
Store at controlled room temperature
15° to 30° C (59° to 86° F), protected from moisture.
CAUTION: Federal (U.S.A.) law prohibits
dispensing without prescription.
500 Capsules
Each capsule contains:
Cefaclor USP (monohydrate) equivalent to
250 mg anhydrous cefaclor.
Dispense in a tight, light-resistant container.
Manufactured for: Ranbaxy Pharmaceuticals, Inc.
Raleigh, NC 27612, U.S.A.
Manufactured by: Ranbaxy Laboratories Ltd.
New Delhi-110 019, India
Keep tightly closed.
Usual Adult dosage - 250 mg
three times a day. For severe infections,
this dosage may be doubled.
See literature for complete dosage information.
Lot
Exp
28

250 mg

R RANBAXY

CEFACLOR

Capsules USP

R RANBAXY

NDC 63304-658-80

CEFACLOR

Capsules USP

250 mg

100 Unit-Dose Capsules

Each capsule contains:
Cefaclor USP (monohydrate) equivalent to 250 mg anhydrous cefaclor.

Store at controlled room temperature 15° to 30° C (59° to 86° F), protected from moisture.

Keep tightly closed.

Usual Adult Dosage - 250 mg three times a day. For severe infections, this dosage may be doubled.
See literature for complete dosage information.

Dispense in a tight, light-resistant container.

R RANBAXY

NDC 63304-658-80

CEFACLOR

Capsules USP

250 mg

100 Unit-Dose Capsules

CAUTION : Federal dispensing without

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Manufactured for : I
Raleigh, NC 27612,
Manufactured by : R
New Delhi-110 019,

Lot:

Exp:

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anhydrous cefaclor.

controlled room temperature
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from moisture.

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in a tight, light-resistant

RANBAXY

NDC 63304-658-80

CEFACLOR

Capsules USP

250 mg

100 Unit-Dose Capsules

CAUTION : Federal (U.S.A.) law prohibits dispensing without prescription.

This unit-dose package is not child-resistant.

Manufactured for : Ranbaxy Pharmaceuticals Inc.
Raleigh, NC 27612, U.S.A.
Manufactured by : Ranbaxy Laboratories Limited
New Delhi-110 019, India

Lot:

Exp:

500 mg

CEFACLOR

Capsules USP

R RANBAXY

R RANBAXY

NDC 63304-659-80

CEFACLOR

Capsules USP

500 mg

100 Unit-Dose Capsules

Each capsule contains:
Cefaclor USP (monohydrate) equivalent to 500 mg anhydrous cefaclor.

Store at controlled room temperature 15° to 30°C (59° to 86° F), protected from moisture.

Keep tightly closed.

Usual Adult Dosage - 250 mg three times a day. For severe infections, this dosage may be doubled.
See literature for complete dosage information.

Dispense in a tight, light-resistant container.

R RANBAXY

NDC 63304-659-80

CEFACLOR

Capsules USP

500 mg

100 Unit-Dose Capsules

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Raleigh
Manufa
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Lot:

Exp

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RANBAXY

NDC 63304-659-80

CEFACLOR

Capsules USP

500 mg

100 Unit-Dose Capsules

CAUTION : Federal (U.S.A.) law prohibits dispensing without prescription.

This unit-dose package is not child-resistant.

Manufactured for : Ranbaxy Pharmaceuticals Inc.
Raleigh, NC 27612, U.S.A.
Manufactured by : Ranbaxy Laboratories Limited
New Delhi-110 019, India

Lot:

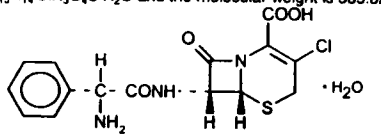
Exp:

CEFACLOR CAPSULES USP

CEFACLOR CAPSULES USP

DESCRIPTION

Cefaclor, USP is a semisynthetic cephalosporin antibiotic for oral administration. It is chemically designated as 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate. The chemical formula for cefaclor is $C_{15}H_{14}ClN_3O_4S \cdot H_2O$ and the molecular weight is 385.82.



Each capsule contains cefaclor monohydrate equivalent to 250 mg (0.68 mmol) or 500 mg (1.36 mmol) anhydrous cefaclor. The capsules also contain pregelatinized starch, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, gelatin, FD&C Blue No. 1, D&C Yellow No. 10, FD&C Red No. 40, D&C Red No. 28, titanium dioxide, sicomet black oxide and edible printing ink.

CLINICAL PHARMACOLOGY

Cefaclor is well absorbed after oral administration to fasting subjects. Total absorption is the same whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed when the drug is administered to fasting subjects and generally appears from three fourths to 1 hour later. It has been reported that following administration of 250-mg, 500-mg, and 1-g doses to fasting subjects, average peak serum levels of approximately 7, 13, and 23 mcg/mL respectively were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in the urine within 8 hours, the greater portion being excreted within the first 2 hours. During this 8-hour period, peak urine concentrations following the 250-mg, 500-mg and 1-g doses were approximately 600, 900 and 1,900 mcg/mL respectively. The serum half-life in normal subjects is 0.6 to 0.9 hour. In patients with reduced renal function, the serum half-life of cefaclor is slightly prolonged. In those with complete absence of renal function, the plasma half-life of the intact molecule is 2.3 to 2.8 hours. Excretion pathways in patients with markedly impaired renal function have not been determined. Hemodialysis shortens the half-life by 25% to 30%.

Microbiology - *In vitro* tests demonstrate that the bactericidal action of the cephalosporins results from inhibition of cell-wall synthesis. Cefaclor has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobes, Gram-positive
- Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes* (group A β-hemolytic streptococci)

Aerobes, Gram-negative
- *Escherichia coli*
- *Haemophilus influenzae*, including β-lactamase-producing ampicillin-resistant strains
- *Klebsiella* sp
- *Proteus mirabilis*

The following *in vitro* data are available, **but their clinical significance is unknown.**

Cefaclor exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤ 8 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefaclor in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobes, Gram-negative
- *Citrobacter diversus*
- *Moraxella (Branhamella) catarrhalis*
- *Neisseria gonorrhoeae*

Anaerobes, Gram-positive
- *Bacteroides* sp (excluding *Bacteroides fragilis*)
- Peptococci
- Peptostreptococci
- *Propionibacterium acnes*

Note:Pseudomonas sp, *Acinetobacter calcoaceticus* (formerly *Mima* sp and *Herellea* sp), and most strains of enterococci (*Enterococcus faecalis*[formerly *Streptococcus faecalis*], group D streptococci), *Enterobacter* sp, indole-positive *Proteus*, and *Serratia* sp are resistant to cefaclor. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cefaclor and methicillin-type antibiotics.

Disk Susceptibility Tests

Diffusion Techniques - Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[1] that has been recommended for use with disks to test the susceptibility of microorganisms to cefaclor uses the 30-mcg cefaclor disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefaclor. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels can be obtained or if high dosage is used.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-mcg cefaclor disk should be interpreted according to the following criteria :

Zone diameter (mm)	Interpretation
≥ 18	Susceptible (S)
15 - 17	Intermediate (I)
≤ 14	Resistant (R)

When Testing *H. influenzae**

Zone diameter (mm)	Interpretation
≥ 20	Susceptible (S)
17 - 19	Intermediate (I)
≤ 16	Resistant (R)

* Disk susceptibility tests performed using Haemophilus Test Medium (HTM)[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (*See* CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 30-mcg cefaclor disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganisms	Zone Diameter (mm)
E. coli ATCC 25922	23 - 27
S. aureus ATCC 25923	27 - 31

When Testing *H. influenzae**

Microorganisms	Zone Diameter (mm)
H. influenzae ATCC 49766	25 - 31

* Disk susceptibility tests performed using Haemophilus Test Medium (HTM)[1]

Dilution Techniques -- Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds.

One such standardized procedure uses a standardized dilution method[2] (broth, agar, or microdilution) or equivalent with cefaclor powder. The MIC v interpreted according to the foll

MIC (mcg/mL)
≤ 8
16
≥ 32

Interpretation should be as sta diffusion techniques.

As with standard diffusion tec require the use of laboratory Standard cefaclor powder should values:

Microorganism
E. coli ATCC 25922
E. faecalis ATCC 29212
S. aureus ATCC 29213

When Testing *H.*

Microorganism
H. Influenzae ATCC 49247

* Broth microdilution tests perfor Test Medium (HTM)[2]

INDICATIONS AN

Cefaclor is indicated in the tr infections when caused by sus designated microorganisms:

- Otitis media caused by *S. pn* staphylococci, and *S. pyoge* streptococci)
- Lower respiratory infections caused by *S. pneumoniae* *pyogenes* (group A β-hemo
- Upper respiratory infections, i tonsillitis, caused by *S.* β-hemolytic streptococci)
  - *Note*: Penicillin is the usu treatment and prevention of including the prophylaxis of r is generally effective in the er from the nasopharynx; how establishing the efficacy of ce prevention of rheumatic fev present.
- Urinary tract infections, includ cystitis, caused by *E. coli*, *P.* and coagulase-negative stap
- Skin and skin structure in *Staphylococcus aureus* and β-hemolytic streptococci)

Appropriate culture and susceptit performed to determine susceptit organism to cefaclor.

CONTRAINDICAT

Cefaclor is contraindicated in patie to the cephalosporin group of antibi

Aerobes, Gram-positive
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains
Streptococcus pneumoniae
Streptococcus pyogenes (group A β-hemolytic streptococci)
Aerobes, Gram-negative
Escherichia coli
Haemophilus influenzae, including β-lactamase-producing ampicillin-resistant strains
Klebsiella sp
Proteus mirabilis

The following *in vitro* data are available, **but their clinical significance is unknown.**

Cefaclor exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤ 8 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefaclor in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobes, Gram-negative
Citrobacter diversus
Moraxella (Branhamella) catarrhalis
Neisseria gonorrhoeae
Anaerobes, Gram-positive
Bacteroides sp (excluding *Bacteroides fragilis*)
Peptococci
Peptostreptococci
Propionibacterium acnes

Note: *Pseudomonas* sp, *Acinetobacter calcoaceticus* (formerly *Mima* sp and *Herellea* sp), and most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*], group D streptococci), *Enterobacter* sp, indole-positive *Proteus*, and *Serratia* sp are resistant to cefaclor. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cefaclor and methicillin-type antibiotics.

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Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-mcg cefaclor disk should be interpreted according to the following criteria :

Zone diameter (mm)	Interpretation
≥ 18	Susceptible (S)
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≤ 14	Resistant (R)

When Testing *H. influenzae**

Zone diameter (mm)	Interpretation
≥ 20	Susceptible (S)
17 - 19	Intermediate (I)
≤ 16	Resistant (R)

* Disk susceptibility tests performed using Haemophilus Test Medium (HTM)[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (*See* CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 30-mcg cefaclor disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganisms	Zone Diameter (mm)
E. coli ATCC 25922	23 - 27
S. aureus ATCC 25923	27 - 31

When Testing *H. influenzae**

Microorganisms	Zone Diameter (mm)
H. influenzae ATCC 49766	25 - 31

* Disk susceptibility tests performed using Haemophilus Test Medium (HTM)[1]

Dilution Techniques -- Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds.

One such standardized procedure uses a standardized dilution method[2] (broth, agar, or microdilution) or equivalent with cefaclor powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

Interpretation should be as stated above for results using diffusion techniques.

As with standard diffusion techniques, dilution methods require the use of laboratory control microorganisms. Standard cefaclor powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
E. coli ATCC 25922	1 - 4
E. faecalis ATCC 29212	> 32
S. aureus ATCC 29213	1 - 4

When Testing *H. Influenzae**

Microorganism	MIC (mcg/mL)
H. Influenzae ATCC 49247	0.12 - 0.5

* Broth microdilution tests performed using Haemophilus Test Medium (HTM)[2]

INDICATIONS AND USAGE

Cefaclor is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Otitis media caused by *S. pneumoniae*, *H. influenzae*, staphylococci, and *S. pyogenes* (group A β-hemolytic streptococci)

Lower respiratory infections, including pneumonia, caused by *S. pneumoniae*, *H. influenzae*, and *S. pyogenes* (group A β-hemolytic streptococci)

Upper respiratory infections, including pharyngitis and tonsillitis, caused by *S. pyogenes* (group A β-hemolytic streptococci)

Note: Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefaclor is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cefaclor in the subsequent prevention of rheumatic fever are not available at present.

Urinary tract infections, including pyelonephritis and cystitis, caused by *E. coli*, *P. mirabilis*, *Klebsiella* sp, and coagulase-negative staphylococci

Skin and skin structure infections caused by *Staphylococcus aureus* and *S. pyogenes* (group A β-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefaclor.

CONTRAINDICATIONS

Cefaclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including cefaclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

PRECAUTIONS

General - If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, eg, pressor amines, antihistamines or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Since the half-life of cefaclor in anuria is 2.3 to 2.8 hours, dosage adjustments for patients with moderate or severe renal impairment are usually not required. Clinical experience with cefaclor under such conditions is limited; therefore, careful clinical observation and laboratory studies should be made.

As with other β-lactam antibiotics, the renal excretion of cefaclor is inhibited by probenecid.

As a result of administration of cefaclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape (Glucose Enzymatic Test Strip, USP).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Pregnancy - Pregnancy Category B - Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given 3 times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers - Small amounts of cefaclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/mL, at 2, 3, 4, and 5 hours respectively. Trace amounts were detected at 1 hour. The effect on nursing infants is not known. Caution should be exercised when cefaclor is administered to a nursing woman.

Pediatric Use - Safety and effectiveness of this product for use in pediatric patients less than 1 month of age have not been established.

ADVERSE REACTIONS

Adverse effects considered to be related to therapy with cefaclor are listed below:

Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' test each occur in less than 1 in 200 patients.

Cases of **serum-sickness-like** reactions have been reported with the use of cefaclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. Occasionally, solitary symptoms may occur, but do not represent a **serum-sickness-like reaction**. While further investigation is ongoing, **serum-sickness-like** reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with cefaclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = 2 to 3 days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.

More severe hypersensitivity reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylactoid events may be manifested by solitary symptoms including angioedema, asthenia, edema (including face and limbs), dyspnea, paresthesias, syncope, hypotension or vasodilatation. Anaphylaxis may be more common in patients with a history of penicillin allergy.

Rarely, hypersensitivity symptoms may persist for several months.

Gastrointestinal symptoms occur in about 2.5% of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Other effects considered related to therapy included eosinophilia (1 in 50 patients), genital pruritus or vaginitis (less than 1 in 100 patients), and, rarely, thrombocytopenia or reversible interstitial nephritis.

Causal Relationship Uncertain --

CNS-Rarely, reversible hyperactivity, agitation, nervousness, insomnia, confusion, hypertonia, dizziness, hallucinations, and somnolence have been reported.

Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic - Slight elevations of AST (SGOT), ALT (SGPT), or alkaline phosphatase values (1 in 40).

Hematopoietic - As has also been reported with other β-lactam antibiotics, transient lymphocytosis, leukopenia, and rarely, hemolytic anemia and reversible neutropenia of possible clinical significance.

There have been rare reports of increased prothrombin time with or without clinical bleeding in patients receiving cefaclor and Coumadin concomitantly.

Renal - Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

OVERDOSAGE

Signs and Symptoms - The toxic symptoms following an overdose of cefaclor may include nausea, vomiting, epigastric distress, and diarrhea. The severity of the epigastric distress and the diarrhea are dose related. If other symptoms are present, it is probable that they are secondary to an underlying disease state, an allergic reaction, or the effects of other intoxication.

Treatment -- To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Unless 5 times the normal dose of cefaclor has been ingested, gastrointestinal decontamination will not be necessary.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cefaclor.

DOSAGE AND ADMINISTRATION

Cefaclor is administered orally.

Adults - The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia) or those caused by less susceptible organisms, doses may be doubled.

Children - The usual recommended daily dosage for children is 20 mg/kg/day in divided doses every 8 hours. In more serious infections, otitis media, and infections caused by less susceptible organisms, 40 mg/kg/day are recommended, with a maximum dosage of 1 g/day.

Cefaclor may be administered in the presence of impaired renal function. Under such a co
is unchanged (see PRECAUTI

In the treatment of β-hemolyt
a therapeutic dosage of cefacl
for at least 10 days.

HOW SUPI

Capsules:

250 mg, blue and green, pr
(100s) NDC 63304-658-0
(250s) NDC 63304-658-0-
(500s) NDC 63304-658-05
(unit-dose 100s) NDC 633

500 mg, blue and green, prin
(100s) NDC 63304-659-01
(250s) NDC 63304-659-04
(500s) NDC 63304-659-05
(unit-dose 100s) NDC 633

*Store at controlled room te
(59° to 86° F), protected from
CAUTION-Federal (USA) law pr
prescription.

REFERENC

1. National Committee for Clinic
Performance standards f
susceptibility tests - 5th ed
NCCLS Document M2-A5, V
Villanova, PA, 1993.
2. National Committee for Clinica
Methods for dilution antimicro
for bacteria that grow aerobica
Standard NCCLS Document
NCCLS, Villanova, PA, 1993.

Revised : May, 1997

Manufactured for :
Ranbaxy Pharmaceuticals Inc
Raleigh, NC 27612, U.S.A.

Manufactured by :
Ranbaxy Laboratories Limited
New Delhi-110 019, India

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Cefaclor may be administered in the presence of impaired renal function. Under such a condition, the dosage usually is unchanged (see PRECAUTIONS).

In the treatment of β-hemolytic streptococcal infections, a therapeutic dosage of cefaclor should be administered for at least 10 days.

HOW SUPPLIED

Capsules:

250 mg, blue and green, printed "RX 658" -
(100s) NDC 63304-658-01;
(250s) NDC 63304-658-04;
(500s) NDC 63304-658-05;
(unit-dose 100s) NDC 63304-658-80

500 mg, blue and green, printed "RX 659" -
(100s) NDC 63304-659-01;
(250s) NDC 63304-659-04;
(500s) NDC 63304-659-05;
(unit-dose 100s) NDC 63304-659-80

"Store at controlled room temperature 15° to 30° C (59° to 86° F), protected from moisture."

CAUTION-Federal (USA) law prohibits dispensing without prescription.

REFERENCES

1. National Committee for Clinical Laboratory Standards, Performance standards for antimicrobial disk susceptibility tests - 5th ed., Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.
2. National Committee for Clinical Laboratory Standards, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - 3rd ed., Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA, 1993.

Revised : May, 1997

Manufactured for :
Ranbaxy Pharmaceuticals Inc.
Raleigh, NC 27612, U.S.A.

Manufactured by :
Ranbaxy Laboratories Limited
New Delhi-110 019, India

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64156

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4

2. AADA # 64-156

3. NAME AND ADDRESS OF APPLICANT

Headquarters:

Ranbaxy Laboratories Limited
Registered Office:
Sahibzada Ajit Singh Nagah
160 055 Distt Ropar (Punjab)

Manufacturing Facility:

Manufacturing, packaging and labeling, testing:

Ranbaxy Laboratories Limited
Industrial Area No. 3
Dewas: 455 001
Madhya Pradesh, India

U.S. Agent:

Ranbaxy Pharmaceuticals Inc.
Jim Sibert, Executive Director
4600 Marriott Drive
Suite 100
Raleigh, NC 27612

4. LEGAL BASIS for ANDA SUBMISSION
21 CFR 442.104

5. SUPPLEMENT(s)
N/A

6. NAME OF DRUG
Cefaclor

7. NONPROPRIETARY NAME
Cefaclor

8. SUPPLEMENT(s) PROVIDE(s) FOR
N/A

9. AMENDMENTS AND OTHER DATES

Firm:

1.	Original submission	7/5/95
2.	Major amendment	3/22/96
3.	GC regarding minor correction to amendment	4/8/96
4.	Bioequivalence amendment	6/19/96
5.	Correspondence to #4	6/26/96
6.	GC with notice of intent to respond to Chem. Def.#2	9/17/96
7.	GC re: Bio issues	10/10/96
8.	Bioequivalence amendment	11/12/96
9.	" " " " " " - Addendum to #8 above	12/4/96
10.	Minor amendment	3/24/97
11.	Minor amendment (telephone amendment)	5/2/97
12.	**Minor amendment***	5/27/97

*** Amendment being reviewed**

FDA:

1.	Acknowledgement letter	9/20/95
2.	Chemistry review #1, deficiency letter	12/19/95
3.	Bio review #1, deficiency letter	1/18/96
4.	Labelling review #1	10/26/96
5.	Labelling review #2	5/6/96
6.	Chemistry review #2, deficiency letter: **MINOR**	9/12/96
7.	Fax re: Bio issues	9/19/96
8.	Telecons re: Bio issues	10/17, 10/23/96
9.	Bio review #2, deficiency letter	1/15/97
10.	Labelling deficiency letter	4/1/97
11.	Chem. Rev. #3, deficiencies faxed	4/29/97
12.	**Labelling** rev. of 5/27/97 submission- **acceptable**	6/11/97
13.	**Bio** review #3 - **acceptable**	6/12/97
14.	**Sample analysis** results - **acceptable**	7/18/97

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. HOW DISPENSED
℞

12. RELATED IND/NDA/DMF(s)

DMF'S:

AADA 64-105 (bulk cefaclor - Ranbaxy

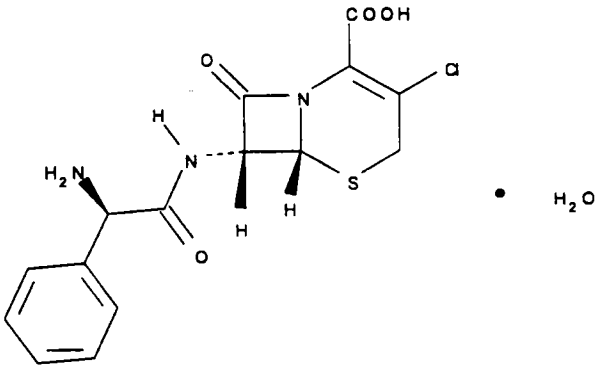
13. DOSAGE FORM
Capsule

14. POTENCY
250 and 500 mg

15. CHEMICAL NAME AND STRUCTURE

Cefaclor USP

$C_{15}H_{14}ClN_3O_4S.H_2O$; M.W. = 385.82



3-Chloro-7-*D*-(2-phenylglycinamido)-3-cephem-4-carboxylic acid monohydrate. CAS [70356-03-5]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The firm responded to our deficiency letter of May 2, 1997 with a **Minor**

Amendment. The only CMC issue was a comment regarding the stability data reporting form:

Deficiency:

1. Please revise your stability data reporting form to include the date upon which the assays were performed.

Response:

The stability data reporting form was revised as requested and the revised form was provided a Attachment 1.

Acceptable

- **Labelling:** Acceptable per 6/11/97 review

- **Bio:** The firm responded to the latest bio deficiency letter in a May 2, 1997 amendment which was found acceptable in a 6/11/97 review and communicated to the firm in a 6/12/97 letter.

- **Sample analysis:** The analysis of samples sent to the FDA laboratory on May 8, 1997 was completed and found acceptable in a 7/18/97 report.

- **Bulk Drug Substance:** Ranbaxy AADA 64-105 - Facsimile amendment submitted 1/3/97, acceptable. Application approved **(insert date).**

Outstanding issues are:

- **EER:** EER pending as of May 28, 1997.

18. CONCLUSIONS:

This application is approvable.(**pending reeeipt of an acceptable EER.)** .

19. **REVIEWER**
R.C.Adams

DATE COMPLETED
6/25/97

INGREDIENT	*250MG* QTY/CAP (MG)	*% of Total Fill Wt.* %W/W	*500MG* QTY/CAP (MG)	*CAPSULE* %W/W
Cefaclor Monohydrate USP	267.5[1]	89.8	535[2]	89.8
Pregelatinized Starch, NF[3]				
Colloidal Silicon Dioxide, NF				
Magnesium Stearate NF				
Croscarmellose Sodium, NF				
Capsule shell	Size "2"; Blue/green printed with two parallel lines in black edible ink on both cap and body	N/A	Size "0-el"; Blue/green printed with two parallel lines in black edible ink on both cap and body	
TOTALS	**298.0**	**100.1**	**596.0**	**100.1**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 64156

BIOEQUIVALENCE REVIEW(S)

D.N

AADA 64-156

JAN 15 1997

Ranbaxy Pharmaceuticals, Inc.
Attention: Jim Siebert
4600 Marriott Drive - Suite 100
Raleigh NC 27612

Dear Sir:

Reference is made to the Abbreviated Antibiotic Drug Application amendments submitted on June 19 and 26, October 23, November 12, and December 4, 1996 for Cefaclor Capsules USP, 250mg and 500mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The bioequivalence studies, both fasting and non-fasting, are unacceptable.

2. It was found that the nominal concentrations of the standard curve samples and control samples were adjusted upward by approximately 10% over the nominal concentrations reported in the original submissions. These adjustments for the standard curves and control samples should not be made once the analytical work is completed unless new solutions were used for the standard curves and control samples. No new solutions were used for either the standards or the control samples. The studies are not acceptable due to the unacceptable analytical procedure used.

3. The batch numbers given in the submission is identical for both the 250 mg and the 500 mg strengths. Is this a typographical error?

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address **all** of the comments presented in this letter. Should you have any questions, please call A. Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DN DEC 27 1996

Cefaclor Capsules

250 mg and 500 mg Capsules

AADA #64156

Reviewer: Moo Park

Filename: 64156a.696

Ranbaxy Laboratories

Raleigh, NC

Submission Date:
June 19, 1996
June 26, 1996
October 23, 1996
November 12, 1996
December 4, 1996

Review of Five Amendments

I. Objective

Review of Ranbaxy's responses to the Agency's deficiency letter dated January 18, 1996. Cursory review of the amendments revealed a fatal flaw in the assay validation and it was decided that detailed review of the amendments was not necessary.

II. Comments

1. Five deficiencies were listed in the Agency letter dated 1/18/96 as follows:

   (1). Assay method validation: The use of degradation factor to adjust the assay data of plasma samples is not an acceptable practice.

   (2). Assay and content uniformity data for the test and reference products for the 250 mg and 500 mg strengths should be submitted.

   (3). Comparative dissolution data of the test and reference products for the 250 mg strength should be submitted.

   (4). Batch size (yield) of the bio-batch and executed batch

record should be submitted.

(5). The batch number for the test product given in the submission is identical for the 250 mg and 500 mg strengths. Is this a typographical error?

2. The firm responded to question (1) revealing questionable practice in analytical procedure. Further discussion will be given in the next section.

3. It was found in the cursory review of the amendments that the questions (2), (3) and (4) were answered properly by the applicant.

4. Question (5) was not answered.

III. Question on Assay Validation

The firm applied a correction factor called degradation factor in the calculation of plasma levels of the fasting and nonfasting studies. The firm was told by the Agency that the correction factor should not be used.

The firm eliminated the correction factor in the calculation of the plasma cefaclor levels for the amendments and as a result all the plasma data show approximately 10% higher values than the original levels reported in the original studies submission. The firm simply recalculated the original data for the standard curves, control samples and unknown plasma samples.

The firm was requested to submit assay validation data for the amendments where the correction factor was eliminated from the cefaclor level calculations. The firm's amendment dated October 23, 1996 showed that the nominal concentrations for the control samples were adjusted upward by approximately 10% over the nominal concentrations reported in the original submissions. It was also found that the nominal concentrations of the standard curve samples were also adjusted upward by approximately 10% over the nominal concentrations reported in the original submissions.

These adjustments for the standard curves and control samples should not be made once the analytical work is completed unless new solutions were used for the standard curves and control

samples. The firm did not use any new solutions for the standards and control samples. Validation of analytical method implicates that the analytical work is supposed to be done while the standard curve samples, control samples and unknown plasma samples are still stable. Therefore, the use of degradation factor or the change of nominal concentrations for the standards and control samples should not be practiced.

IV. Deficiencies

1. It was found that the nominal concentrations of the standard curve samples and control samples were adjusted upward by approximately 10% over the nominal concentrations reported in the original submissions. These adjustments for the standard curves and control samples should not be made once the analytical work is completed unless new solutions were used for the standard curves and control samples. The firm did not use any new solutions for the standards and control samples. The studies are not acceptable due to the unacceptable analytical procedure used.

2. The batch number for the test product given in the submission is identical for the 250 mg and 500 mg strengths. Is this a typographical error?

V. Recommendation

The two bioequivalence studies conducted under fasting and non-fasting conditions by Ranbaxy Laboratories on its Cefaclor Capsules, USP, 500 mg, lot #P00194 comparing it to Eli Lilly's Ceclor^{R}, 500 mg, lot #8AA88A, and reviewed previously (submission date: 7/7/95; review date: 12/18/95) have been found unacceptable by the Division of Bioequivalence.

The firm should be informed of the recommendation and deficiencies.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

DW

AADA 64-156

JUN 12 1997

Ranbaxy Pharmaceuticals, Inc.
Attention: Jim Siebert
4600 Marriott Drive - Suite 100
Raleigh NC 27612

Dear Sir:

Reference is made to your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act for Cefaclor Capsules USP, 250 mg and 500 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

6/12/1997

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 1 1 1997

Cefaclor Capsules

250 mg and 500 mg Capsules

AADA #64156

Reviewer: Moo Park

Filename: 64156a.297

Ranbaxy Laboratories

Raleigh, NC

Submission Date:
February 21, 1997
May 2, 1997

Review of an Amendment

I. Objective

Review of Ranbaxy's responses to the Agency's deficiency letter dated January 15, 1997.

II. Background

Ranbaxy's original submission of its bioequivalence studies for Cefaclor Capsules under fasting and nonfasting conditions (submission date: 7/7/1995) had five deficiencies including the use of degradation factor to adjust the assay data of plasma samples. The agency told Ranbaxy that the use of the degradation factor was not acceptable in a deficiency letter dated 1/18/1996.

Ranbaxy submitted five amendments (review date: 12/27/1996). The firm revised the data for plasma cefaclor levels, standard curve samples and quality control samples by approximately 10%. The firm did not fully explain how the degradation factor was applied and how the factor could be removed without affecting the integrity of the *in vivo* bioequivalence studies. Ranbaxy was informed that the studies were incomplete in a deficiency letter dated 1/15/97. There was a conference call between FDA and (CRO for Ranbaxy). The firm submitted two amendments for review (submission dates: 2/21/97 and 5/2/97).

III. Comments

FDA's questions and Ranbaxy's response are as follows:

Q1. It was found that the nominal concentrations of the standard curve samples and control samples were adjusted upward by approximately 10% over the nominal concentrations reported in the original submissions. These adjustments for the standard curves and control samples should not be made once

the analytical work is completed unless new solutions were used for the standard curves and control samples. The firm did not use any new solutions for the standards and control samples. The studies are not acceptable due to the unacceptable analytical procedure used.

A1.

Q2. The batch number for the test product given in the submission is identical for the 250 mg and 500 mg strengths. Is this a typographical error?

A2. The common batch number was used because the two strength capsules were manufactured from the same blend. The firm stated that unique numbering system will be used for all commercial production for US market.

IV. Reevaluation of Study Results—

The removal of correction factors increased all the plasma levels by approximately 10% over the data originally submitted. The

firm recalculated all the plasma levels and PK parameters, AUCT, AUCI, CMAX, TMAX, KE and THALF.

A. Study under fasting conditions

A total of 26 subjects enrolled in and completed the study. However, only 24 subjects (Subjects #1-24) were used in the assay and subsequent pharmacokinetic and statistical data analyses following the protocol.

1. Mean plasma levels

Mean plasma cefaclor levels for the test and reference products are similar at all sampling time points as shown in Table 1 and Fig P-1. The mean peak cefaclor levels for the test and reference products were 18.9 mcg/mL and 17.7 mcg/mL, respectively, at 0.75 hour.

TABLE 1. MEAN PLASMA CEFACLOR LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST; MEAN2=REFERENCE; SD=STD DEVIATION; RMEAN12=TEST/REF RATIO
UNIT: MCG/ML

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.01	0.05	0.00	0.00	.
0.25	1.05	1.88	0.73	1.26	1.43
0.5	12.48	8.26	11.96	7.89	1.04
0.75	18.91	6.97	17.69	8.19	1.07
1	16.40	5.01	16.19	6.50	1.01
1.25	12.40	3.69	12.74	4.61	0.97
1.5	9.16	3.61	9.73	3.75	0.94
2	4.54	2.25	5.86	3.44	0.77
3	1.84	1.97	1.94	1.35	0.95
4	0.71	0.55	0.74	0.31	0.97
5	0.35	0.25	0.33	0.16	1.03
6	0.15	0.19	0.12	0.15	1.24
8	0.03	0.10	0.04	0.08	0.93

2. Pharmacokinetic parameters

The pharmacokinetic parameters listed in Table 2 are comparable between the test and reference products. The test/reference ratios for the non-transformed and log-transformed AUCT, AUCI and CMAX range 0.97-1.01. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were with 80-125% as shown in Table 3.

Log-transformed CMAX showed a significant period effect.

TABLE 2. ARITHMETIC MEANS AND RATIOS
MEAN1=TEST; MEAN2=REFERENCE; SD=STD DEVIATION; RMEAN12=TEST/REF RATIO
UNIT: AUC=HR MCG/ML; CMAX=MCG/ML; KE=1/HR; THALF=HR

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	25.45	3.25	26.24	4.40	0.97
AUCT	25.15	3.28	25.94	4.39	0.97
CMAX	21.24	5.14	21.24	5.88	1.00
KE	0.96	0.19	0.97	0.17	1.00
LAUCI	25.25	0.13	25.91	0.16	0.97
LAUCT	24.95	0.13	25.60	0.16	0.97
LCMAX	20.59	0.27	20.33	0.32	1.01
THALF	0.76	0.19	0.74	0.15	1.02
TMAX	0.89	0.51	0.97	0.37	0.91

TABLE 3. LSMEANS AND 90% CONFIDENCE INTERVALS
LSM1=TEST; LSM2=REFERENCE; RLSM12=TEST/REF RATIO
LOWCI12=LOWER 90% CI; UPPCI12=UPPER 90% CI

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	25.45	26.24	0.97	92.46	101.47
AUCT	25.15	25.94	0.97	92.44	101.46
CMAX	21.24	21.24	1.00	89.91	110.10
LAUCI	25.25	25.91	0.97	93.54	101.58
LAUCT	24.95	25.60	0.97	93.51	101.56
LCMAX	20.59	20.33	1.01	90.85	112.87

B. Study under non-fasting conditions

A total of 18 subjects enrolled in and completed the study. All 18 subjects were used in the assay and subsequent pharmacokinetic and statistical data analyses following the protocol.

1. Mean plasma levels

The plasma levels for the 3-way study summarized in Table 4 and Fig P-2. The food effect was very clear. The peak plasma levels for the test and reference products under non-fasting conditions (7.87-8.77 mcg/mL) were approximately 1/2 of the peak plasma level (16.1 mcg/mL) for the test product under fasting conditions. Time to the peak plasma level under non-fasting conditions was approximately 2 hours vs 0.75 hour for the fasting leg. The test and reference products under non-fasting conditions showed similar plasma cefaclor-time profiles.

TABLE 4. MEAN PLASMA CEFACLOR LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FAST; MEAN2=TEST-FOOD; MEAN3=REFERENCE; SD=STD DEVIATION;
RMEAN23=TEST/REF RATIO UNDER NONFASTING
UNIT: MCG/ML

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.03	0.10	0.02	0.08	0.06	0.20
0.25	0.72	1.16	0.03	0.09	0.08	0.20
0.5	10.87	7.38	0.40	0.70	0.42	0.88
0.75	16.10	7.02	1.48	2.39	1.56	2.37
1	15.09	4.05	3.17	3.99	3.41	4.91
1.25	12.98	3.13	4.86	4.95	5.67	5.07
1.5	9.83	2.84	6.91	4.69	8.63	4.11
2	4.97	1.60	7.87	3.14	8.77	2.78
3	1.73	0.87	5.87	2.90	5.33	2.89
4	0.67	0.31	2.65	2.00	2.24	1.61
5	0.31	0.23	1.04	0.99	0.80	0.65
6	0.10	0.15	0.31	0.35	0.29	0.32
8	0.04	0.10	0.04	0.12	0.06	0.16

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	1.75	0.51	0.29
0.25	23.84	8.96	0.38
0.5	27.49	25.90	0.94
0.75	10.87	10.32	0.95
1	4.77	4.43	0.93
1.25	2.67	2.29	0.86
1.5	1.42	1.14	0.80
2	0.63	0.57	0.90
3	0.30	0.33	1.10
4	0.25	0.30	1.18
5	0.29	0.38	1.30
6	0.33	0.35	1.06
8	0.89	0.56	0.62

2. Pharmacokinetic parameters

The test/reference ratios (RMEAN23) for non-transformed and log-transformed AUCT, AUCI and CMAX under non-fasting conditions were within the range of 0.90-0.98 as shown in TableS 5 and 6 and met the Agency's criteria.

TABLE 5. ARITHMETIC MEANS AND RATIOS
MEAN1=TEST-FAST; MEAN2=TEST-FOOD; MEAN3=REFERENCE; SD=STD DEVIATION;
RMEAN23=TEST/REF RATIO UNDER NONFASTING
UNIT: MCG/ML

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	24.44	4.42	21.24	4.09	21.63	3.31
AUCT	24.06	4.38	20.77	4.05	21.25	3.28
CMAX	19.03	4.84	10.41	2.77	11.59	3.03
KE	0.98	0.20	0.97	0.17	0.97	0.17
LAUCI	24.12	0.16	20.90	0.18	21.41	0.15
LAUCT	23.74	0.16	20.43	0.18	21.03	0.15
LCMAX	18.48	0.25	10.08	0.26	11.23	0.26
THALF	0.74	0.17	0.74	0.15	0.74	0.17
TMAX	0.89	0.26	2.14	0.76	1.94	0.59

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.15	1.13	0.98
AUCT	1.16	1.13	0.98
CMAX	1.83	1.64	0.90
KE	1.01	1.02	1.01
LAUCI	1.15	1.13	0.98
LAUCT	1.16	1.13	0.97
LCMAX	1.83	1.65	0.90
THALF	1.00	0.99	0.99
TMAX	0.42	0.46	1.10

TABLE 6. LSMEANS AND RATIOS
LSM1=TEST-FAST; LSM2=TEST-FOOD; LSM3=REFERENCE-FOOD
RLSM23=TEST/REF RATIO UNDER NONFASTING

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	24.44	21.24	21.63	1.15	1.13	0.98
AUCT	24.06	20.77	21.25	1.16	1.13	0.98
CMAX	19.03	10.41	11.59	1.83	1.64	0.90
LAUCI	24.12	20.90	21.41	1.15	1.13	0.98
LAUCT	23.74	20.43	21.03	1.16	1.13	0.97
LCMAX	18.48	10.08	11.23	1.83	1.65	0.90

V. Deficiency

None.

VI. Recommendation

1. The two bioequivalence studies conducted under fasting and non-fasting conditions by Ranbaxy Laboratories on its Cefaclor Capsules, USP, 500 mg, lot #P00194 comparing it to Eli Lilly's Ceclor®, 500 mg, lot #8AA88A, and reviewed

previously (submission date: 7/7/95; review date: 12/18/95) have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Ranbaxy's Cefaclor Capsules, USP, 500 mg, is bioequivalent to Eli Lilly's Ceclor®, 500 mg.

2. The dissolution testing conducted by Ranbaxy on its Cefaclor Capsules, USP, 500 mg strength, lot#P00194, and 250 mg strength, lot#P00194, is acceptable. The formulation for the 250 mg strength is proportional to the 500 mg strength of the test product which underwent acceptable bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 250 mg capsules of the test product is granted. The 250 mg capsules of the test product is therefore deemed bioequivalent to Eli Lilly's Ceclor®, 500 mg.

3. The USP dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using Apparatus 2(paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of cefaclor in the capsule is dissolved in 30 minutes.

The firm should be informed of the recommendations.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

6/4/97

Concur: Date: 6/11/1997

Nicholas Fleischer, Ph.D.
for Director
Division of Bioequivalence

cc: ANDA # 64-156 (original, duplicate), Park, Drug File, Division File, HFD-650 (Director)

Review history: Draft(5/6/97); Final(6/3/97)

DEC 18 1995

Cefaclor Capsules	Ranbaxy Laboratories
250 mg and 500 mg Capsules	Raleigh, NC
AADA #64156	Submission Date:
Reviewer: Moo Park	July 7, 1995
Filename: 64156SDW.795	

Review of Two BE Studies, Dissolution Data and a Waiver Request

I. Objectives

Review of Ranbaxy's

1. A two way crossover BE study under fasting conditions comparing its test product, Cefaclor Capsules, 500 mg strength, to Eli Lilly's Ceclor^{R} 500 mg Capsules.

2. A three way crossover BE study under fasting/non-fasting conditions comparing its test product, Cefaclor Capsules, 500 mg strength, to Eli Lilly's Ceclor^{R} 500 mg Capsules.

3. Comparative dissolution data of 250 mg and 500 mg capsules.

4. Waiver request on the 250 mg capsules.

II. Background

Cefaclor is a cephalosporin antibiotic which inhibits bacterial cell-wall synthesis in a manner similar to that of penicillin. Cefaclor is used in the treatment of otitis media, lower and upper respiratory infections, urinary tract infections and skin and skin structure infections.

Cefaclor is well absorbed after oral administration in fasting subjects. Total absorption is similar regardless whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed in fasting subjects and generally appears about 1 hour later.

Following administration of 250 mg, 500 mg, and 1 g doses in fasting subjects, average peak serum levels of approximately 7, 13, and 23 ug/mL, respectively, were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in urine within 8 hours, the major portion being excreted within the first 2 hours. The serum elimination half-life in subjects with normal renal function is 0.6 to 0.9 hour. In patients with severely reduced renal function, the plasma elimination half-life of the drug is 2.3 to 2.8 hours.

Currently, cefaclor is marketed by Eli Lilly under the name Ceclor®, 250 mg and 500 mg capsules, and as a powder for reconstitution as suspension for oral administration, 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL and 375 mg/5 mL. The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia), doses may be doubled.

III. Study Details

A. Study under fasting conditions

1. Protocol #940781

2. Applicant: Ranbaxy

3. Study sites:
   Clinical study

   Analytical:

4. Investigators:
   Principal investigator:

   Analytical investigator:

5. Clinical study dates: 11/8/94-11/11/94

   Assay dates: 11/15/94-12/9/94

6. Study design: An open-label, randomized, 2-way crossover study to compare the bioavailability of Ranbaxy 500 mg Cefaclor Capsules and Lilly (Ceclor®) 500 mg Cefaclor Pulvules®. Single, oral 500 mg doses were separated by a washout period of 72 hours.

7. Subject: A total of 26 healthy male volunteers enrolled in and completed the study. The subjects were 18-45 years of age, weighing at least 60 kg, and who were within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983)

   Screening: Medical history, physical examination and the laboratory tests of hematologic, hepatic and renal functions were performed. Only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study.

   Exclusions:

   History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastro-intestinal, endocrine,

immunologic, dermatologic, neurologic or psychiatric disease; More specifically, history or presence any form of bleeding disorder; alcoholism or drug abuse within the last year; hypersensitivity or idiosyncratic reaction to any drug, specially cephalosporin antibiotics or penicillin.; Subjects who have been on an abnormal diet (for whatever reason) during the four weeks preceding the study.; Subjects who, through completion of this study, would have donated in excess of 500 mL of blood in 14 days, 750 mL in 3 months, 1000 mL in 6 months, 1500 mL in 9 months or 2000 mL in one year.; Subjects who have participated in another clinical trial within 28 days of study start.

Prohibitions:

No subject may take medication (including OTC products) for 7 days preceding the study. This prohibition does not include daily vitamin supplements taken in non-therapeutic doses. The consumption of alcohol- or xanthine-containing beverages and foods will be prohibited for 24 hours before dosing and throughout the period of sample collection. Smoking will be prohibited for 2 hours after drug administration due to the frequency of blood draws in the first two hours. If drug therapy other than that specified in the protocol is required during the time of sample collection, or between drug administrations, a decision to continue or discontinue the subject will be made, based on the time the medication was administered and its pharmacology and pharmacokinetics.

8. Product information:
   (a) Test product #1: 500 mg Cefaclor Capsules (Ranbaxy)

   Lot #P00194
   Assay: Not available
   Content uniformity: Not available
   Batch size: Not available

   (b) Reference product: 500 mg Ceclor® Capsules (Eli Lilly)

   Lot #8AA88A
   Assay: Not available
   Content uniformity: Not available
   Expiration date: February, 1997

9. Dosing: 1 x 500 mg capsule with 240 mL water.

10. Food and fluid intake: Subjects fasted overnight before dosing and for 4 hours thereafter. Water was not permitted for 2 hours before and 4 hours after the dose (with the exception of water administrations), but were allowed at all other times. A standard meal was provided at 4 hours after drug administration. To promote urine production, 200 mL of

water, at ambient temperature , were provided at 1, 2 and 3 hours after dosing.

11. Housing: From the evening before dosing until after the 8-hour blood draw.

12. Washout period: 72 hours.

13. Blood samples: Blood samples were collected in Vacutainers containing EDTA before dosing (2 x 5 mL) and at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6 and 8 hours (1 x 5 mL). For each volunteer, the total number of blood draws during the study was 26.

14. Urine samples: Urine was collected pre-dose and over the following collection intervals: 0-1, 1-2, 2-4, 4-6 and 6-8 hours, for possible future analysis.

15. Subject monitoring: Subjects were monitored throughout confinement for adverse reactions to the study formulations and/or procedures.

16. IRB and informed consent: IRB approval and informed consent were obtained before the start of the study.

17. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUC_t, AUC_{inf} and C_{max}.

B. Study under non-fasting conditions

1. Protocol #940782

2. Applicant: Ranbaxy

3. Study sites:
   Clinical study

   Analytical:

4. Investigators:
   Principal investigator:

   Analytical investigator:

5. Clinical study dates: 11/16/94-11/30/94

   Assay dates: 11/15/94-12/9/94

6. Study design: Open-label, randomized, 3-way crossover study to compare 1) the bioavailability of Ranbaxy 500 mg Cefaclor Capsules and Lilly (Ceclor^{R}) 500 mg Cefaclor Pulvules under non-fasting conditions, and 2) to compare the bioavailability of the Ranbaxy 500 mg Cefaclor Capsules under fasting and non-fasting conditions.

7. Subject: 18 healthy adult male volunteers were enrolled and completed the three periods of the study.

8. Product information and dosing:

   Regimen (a): Single oral 500 mg dose, administered with 240 mL of water.

   Regimens (b) and (c): Single oral 500 mg dose, administered with 240 mL of water, 30 minutes after a standard breakfast.

   (a) Test product: 1 x 500 mg Cefaclor Capsules (Ranbaxy) under fasting conditions.

   Lot #P00194

   (b) Test product: 1 x 500 mg Cefaclor Capsules (Ranbaxy) under non-fasting conditions.

   Lot #P00194

   (c) Reference product: 1 x 500 mg Ceclor^{R} Capsules (Eli Lilly) under non-fasting conditions.

   Lot #8AA88A

9. Food and fluid intake:

   Regimen (a): Subjects fasted overnight before dosing and for 4 hours thereafter.

   Regimens (b) and (c): Subjects fasted overnight until 30 minutes prior to their scheduled dosing times, when they were given a standard breakfast.

10. Housing: From the evening before dosing until after the 8-hour blood draw.

11. Washout period: 72 hours.

12. Blood samples: Blood samples were collected in Vacutainers containing EDTA before dosing (2 x 5 mL) and at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6 and 8 hours (1 x 5 mL). For each volunteer, the total

number of blood draws during the study was 39.

13. Urine samples: Urine was collected pre-dose and over the following collection intervals: 0-1, 1-2, 2-4, 4-6 and 6-8 hours, for possible future analysis.

14. Subject monitoring: Subjects were monitored throughout confinement for adverse reactions to the study formulations and/or procedures.

15. IRB and informed consent: IRB approval and informed consent were obtained before the start of the study.

16. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and blood levels at each sampling points. The test/reference ratios were calculated for AUC_t, AUC_{inf} and C_{max}.

IV. Validation of Assay Method for Plasma Samples

2. Study under non-fasting conditions

V. In Vivo Results with Statistical Analysis

A. Study under fasting conditions

A total of 26 subjects enrolled in and completed the study. However, only 24 subjects (Subjects #1-24) were used in the assay and subsequent pharmacokinetic and statistical data analyses following the protocol.

Medical events: Subject #7 (reference product in Period 2) reported loose stool at 2.9 hours and 4.6 hours post-dose. No action was taken.

Protocol deviations: Minor deviations were reported as follows:

(1) Subject #22 consumed 1/2 cup of hot chocolate 22.2 hours prior to Period 2 dosing.

(2) Subject #21 received lunch 16 minutes later than the scheduled time in Period 1.

(3) Subject #21 had the 4-hour blood drawing 6 minutes later than scheduled in Period 1.

1. Mean plasma levels

Mean plasma cefaclor levels for the test and reference products are similar at all sampling time points as shown in Table 8 and Fig P-1. The mean peak cefaclor levels for the test and reference products were 17.6 mcg/mL and 16.7 mcg/mL, respectively, at 0.75

hour.

Table 8 MEAN PLASMA CEFACLOR LEVELS FOR TEST AND REFERENCE PRODUCTS

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	0.01	0.05	0.00	0.00	.
0.25	0.94	1.69	0.66	1.13	1.43
0.5	11.55	8.05	11.04	7.61	1.05
0.75	17.64	7.00	16.66	8.27	1.06
1	14.82	4.67	14.65	6.11	1.01
1.25	11.13	3.32	11.44	4.14	0.97
1.5	8.22	3.24	8.74	3.36	0.94
2	4.08	2.01	5.26	3.09	0.78
3	1.70	1.98	1.74	1.21	0.97
4	0.64	0.49	0.66	0.28	0.97
5	0.31	0.23	0.30	0.14	1.03
6	0.13	0.17	0.11	0.14	1.24
8	0.03	0.09	0.03	0.08	0.93

UNIT: PLASMA LEVEL=MCG/ML TIME=HRS
MEAN1=TEST MEAN; MEAN2=REFERENCE MEAN; RMEAN12=TEST/REF RATIO

2. Pharmacokinetic parameters

The pharmacokinetic parameters listed in Table 9 are comparable between the test and reference products. The test/reference ratios for the non-transformed and log-transformed AUCT, AUCI and CMAX range 0.97-1.01. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were with 80-125% as shown in Table 10.

Log-transformed CMAX showed a significant period effect.

Table 9. Summary of PK Parameters (*ANTILOG CONVERSION)

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	23.15	3.12	23.86	4.18	0.97
AUCT	22.91	3.11	23.60	4.15	0.97
CMAX	19.91	5.49	19.98	6.29	1.00
KE	0.96	0.19	0.97	0.17	1.00
LAUCI*	22.96	0.13	23.53	0.17	0.98
LAUCT*	22.71	0.13	23.27	0.17	0.98
LCMAX*	19.16	0.29	18.92	0.35	1.01
THALF	0.76	0.19	0.74	0.15	1.02
TMAX	0.89	0.51	0.97	0.37	0.91

UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR

Table 10. LSMEANS AND 90% CONFIDENCE INTERVALS

PARAMETER	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCI	23.15	23.86	92.65	101.45
AUCT	22.91	23.60	92.71	101.43
CMAX	19.91	19.98	87.87	111.39
LAUCI*	22.96	23.53	93.77	101.52
LAUCT*	22.71	23.27	93.82	101.50
LCMAX*	19.16	18.92	89.44	114.63

LOWCI12=Lower CI limit; UPPCI12=Upper CI limit

3. Test/reference ratios for individual subjects

Table 11 summarizes the test/reference ratios for the PK parameters for individual subjects. The mean ratios for AUCT, AUCI and CMAX were 0.98, 0.98, 1.09, respectively.

Table 11. Test Product/Reference Product Ratios for Individual Subjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	1						
3	3	1						
4	4	1						
5	5	2						
6	6	2						
7	7	1						
8	8	2						
9	9	1						
10	10	2						
11	11	1						
12	12	1						
13	13	2						
14	14	2						
15	15	1						
16	16	2						
17	17	2						
18	18	1						
19	19	1						
20	20	1						
21	21	2						
22	22	1						
23	23	2						
24	24	2						

Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	24	0.98	0.11	0.67	1.23
RAUCI12	24	0.98	0.11	0.67	1.23
RCMAX12	24	1.09	0.45	0.48	2.43
RTMAX12	24	0.99	0.47	0.25	2.00
RKE12	24	1.01	0.21	0.66	1.63
RTHALF12	24	1.03	0.20	0.62	1.49

B. Study under non-fasting conditions

A total of 18 subjects enrolled in and completed the study. All 18 subjects were used in the assay and subsequent pharmacokinetic and statistical data analyses following the protocol.

Medical events: Fourteen medical events were reported by 7 subjects spread over the three treatment evenly: headache, sweating, rash, etc.

Protocol deviations: Subject #4 did not collect his urine during the 6-8 hour urine collection interval. (Urine was not used for assay.)

1. Mean plasma levels

The plasma levels for the 3-way study summarized in Table 12 and Fig P-2. The food effect was very clear. The peak plasma levels for the test and reference products under non-fasting conditions (7.1-7.9 mcg/mL) were approximately 1/2 of the peak plasma level (14.5 mcg/mL) for the test product under fasting conditions. Time to the peak plasma level under non-fasting conditions was approximately 2 hours vs 0.75 hour for the fasting leg. The test and reference products under non-fasting conditions showed similar plasma cefaclor-time profiles.

Table 12. MEAN PLASMA CEFACLOR LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	MEAN3
TIME HR					
0	0.03	0.09	0.02	0.07	0.06
0.25	0.65	1.04	0.03	0.08	0.07
0.5	9.90	6.93	0.36	0.63	0.38
0.75	14.45	6.30	1.33	2.15	1.40
1	13.55	3.64	2.84	3.58	3.06
1.25	11.66	2.81	4.37	4.45	5.09
1.5	8.82	2.55	6.20	4.21	7.75
2	4.46	1.44	7.06	2.82	7.87
3	1.56	0.78	5.27	2.60	4.78
4	0.60	0.28	2.38	1.80	2.02
5	0.27	0.21	0.93	0.89	0.72
6	0.09	0.14	0.28	0.32	0.26
8	0.03	0.09	0.04	0.11	0.06

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR				
0	0.18	1.75	0.51	0.29
0.25	0.18	23.86	8.73	0.37
0.5	0.79	27.88	26.27	0.94
0.75	2.13	10.87	10.32	0.95
1	4.41	4.77	4.43	0.93
1.25	4.55	2.67	2.29	0.86
1.5	3.69	1.42	1.14	0.80
2	2.50	0.63	0.57	0.90
3	2.59	0.30	0.33	1.10
4	1.44	0.25	0.30	1.18
5	0.58	0.29	0.38	1.30
6	0.29	0.33	0.36	1.08
8	0.15	0.89	0.56	0.63

UNIT: PLASMA LEVEL=MCG/ML TIME=HRS

2. Pharmacokinetic parameters

The test/reference ratios (RMEAN23) for non-transformed and log-transformed AUCT, AUCI and CMAX under non-fasting conditions were within the range of 0.90-0.98 as shown in Table 13 and met the Agency's criteria.

Table 13. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION)

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3
AUCI	21.97	3.99	19.08	3.68	19.43
AUCT	21.64	3.96	18.65	3.64	19.08
CMAX	17.23	4.56	9.35	2.49	10.40
KE	0.98	0.20	0.97	0.17	0.97
LAUCI	21.68	0.16	18.78	0.18	19.23
LAUCT	21.35	0.17	18.35	0.18	18.88
LCMAX	16.70	0.26	9.05	0.26	10.08
THALF	0.74	0.17	0.74	0.15	0.74
TMAX	0.89	0.26	2.14	0.76	1.94

(CONTINUED)

PARAMETER	SD3	RMEAN12	RMEAN13	RMEAN23
AUCI	2.97	1.15	1.13	0.98
AUCT	2.94	1.16	1.13	0.98
CMAX	2.72	1.84	1.66	0.90
KE	0.17	1.01	1.02	1.01
LAUCI	0.15	1.15	1.13	0.98
LAUCT	0.15	1.16	1.13	0.97
LCMAX	0.26	1.84	1.66	0.90
THALF	0.17	1.00	0.99	0.99
TMAX	0.59	0.42	0.46	1.10

UNIT: AUC=MCG HR/ML CMAX=MCG/ML TMAX=HR

VI. Product Information

1. Formulation

The formulations for the 250 mg and 500 mg strengths of the test product are shown in Table . The two formulations are proportional in the active and inactive ingredients. The reference product contains cornstarch and magnesium stearate and

other inactive ingredients besides the active ingredient.

Table 14. Test Formulations

Ingredient	250 mg Capsule, mg	500 mg Capsule, mg
Cefaclor, USP	250 + 2% overage	500 + 2% overage
Pregelatinized Starch, NF		
Colloidal Silicon Dioxide, NF		
Croscarmellose Sodium, NF		
Magnesium Stearate, NF		
Total weight	298	596

2. Assay and content uniformity

Assay and content uniformity data for the test and reference products were not submitted.

VII. Dissolution

Comparative dissolution data for the 500 mg strength are acceptable as summarized in Table 15. However, comparative dissolution data for the 250 mg strength were not submitted. The firm submitted dissolution data for the test 250 mg capsules only.

USP 23 dissolution method for Cefaclor Capsules was used:

Medium: 900 mL water
Apparatus 2: 50 rpm
Tolerance: NLT (Q) in 30 min

VIII. Waiver Request

Waiver request for the 250 mg strength was submitted. The waiver won't be granted at this time.

IX. Comments

1. Assay method validation: The — described two major events in the assay of cefaclor. Both events were observed not during the pre-study validation but during the

within-study assay. The events are:

(a). Endogenous interferences: Predose samples for most of the subjects in the study showed a low level interference at the retention time of cefaclor. asserts that the interference should not affect the study results.

(b). Stability of cefaclor in standard curve samples and QC samples: found that cefaclor in plasma degrades upon each cycle of freeze-thaw during the study. used a factor of degradation, to adjust for the loss of cefaclor in the standards and QC samples. stated that this factor would not change the result of the study because all samples from a given subject were analyzed using the same calibration curve.

2. Study under fasting conditions: Twenty-six (26) subjects enrolled in and completed the study. However, only 24 subjects (Subjects #1-24) were used in the assay and subsequent pharmacokinetic and statistical data analyses following the protocol. Mean plasma cefaclor levels for the test and reference products are similar at all sampling time points. The mean peak cefaclor levels for the test and reference products were 17.6 mcg/mL and 16.7 mcg/mL, respectively, at 0.75 hour. The pharmacokinetic parameters are comparable between the test and reference products. The test/reference ratios for the non-transformed and log-transformed AUCT, AUCI and CMAX range 0.97-1.01. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX were within 80-125%.

3. Study under non-fasting conditions: A total of 18 subjects enrolled in and completed the study. All 18 subjects were used in the assay and subsequent pharmacokinetic and statistical data analyses. The food effect was very clear. The peak plasma levels for the test and reference products under non-fasting conditions (7.1-7.9 mcg/mL) were approximately 1/2 of the peak plasma level (14.5 mcg/mL) for the test product under fasting conditions. Time to the peak plasma level under non-fasting conditions was approximately 2 hours vs 0.75 hour for the fasting leg. The test and reference products under non-fasting conditions showed similar plasma cefaclor-time profiles. The test/reference ratios for non-transformed and log-transformed AUCT, AUCI and CMAX under non-fasting conditions were within the range of 0.90-0.98.

4. No significant adverse reactions were reported during the study.

5. The batch size (yield) of the bio-batch was not submitted.

Intended batch size was capsules.

6. Assay and content uniformity data for the test and reference products for the 250 mg and 500 mg strengths were not submitted.

7. Dissolution data for the 500 mg strength are acceptable. However, comparative dissolution data for the 250 mg should be submitted.

X. Deficiencies

1. Assay method validation: The use of degradation factor to adjust the assay data of plasma samples is not an acceptable practice.

2. Assay and content uniformity data for the test and reference products for the 250 mg and 500 mg strengths should be submitted.

3. Comparative dissolution data of the test and reference products for the 250 mg strength should be submitted.

4. Batch size (yield) of the bio-batch and executed batch record should be submitted.

5. The batch number for the test product given in the submission is identical for the 250 mg and 500 mg strengths. Is this a typographical error?

XI. Recommendation

The two bioequivalence studies conducted under fasting and non-fasting conditions by Ranbaxy Laboratories on its Cefaclor Capsules, USP, 500 mg, lot #P00194 comparing it to Eli Lilly's Ceclor®, 500 mg, lot #8AA88A, has been found incomplete by the Division of Bioequivalence. The firm should submit additional data listed under Comments #1-5.

The firm should be informed of the recommendation and deficiencies.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE _____ 12/15/95

Concur: _____ Date: 12/19/95
Keith Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA # 64-156, HFD-630(OGD), HFD-604(Hare), HFD-658 (Mhatre, Park), HFD-22 (Hooton), HFC-130/JAllen, Drug File

Review history: Draft(11/21/95); Final(12/14/95)

(Please select Typeover for Input.)

Table 15. In Vitro Dissolution Testing

Drug (Generic Name):Cefaclor Capsules
Dose Strength:250 and 500 mg
ANDA No.:64-156
Firm:Ranbaxy
Submission Date:
File Name:

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:x RPM: 50
No. Units Tested: 12
Medium:water Volume: 900 mL
Specifications:NLT in 30 Min
Reference Drug: Eli Lilly's Ceclor Capsules
Assay Methodology

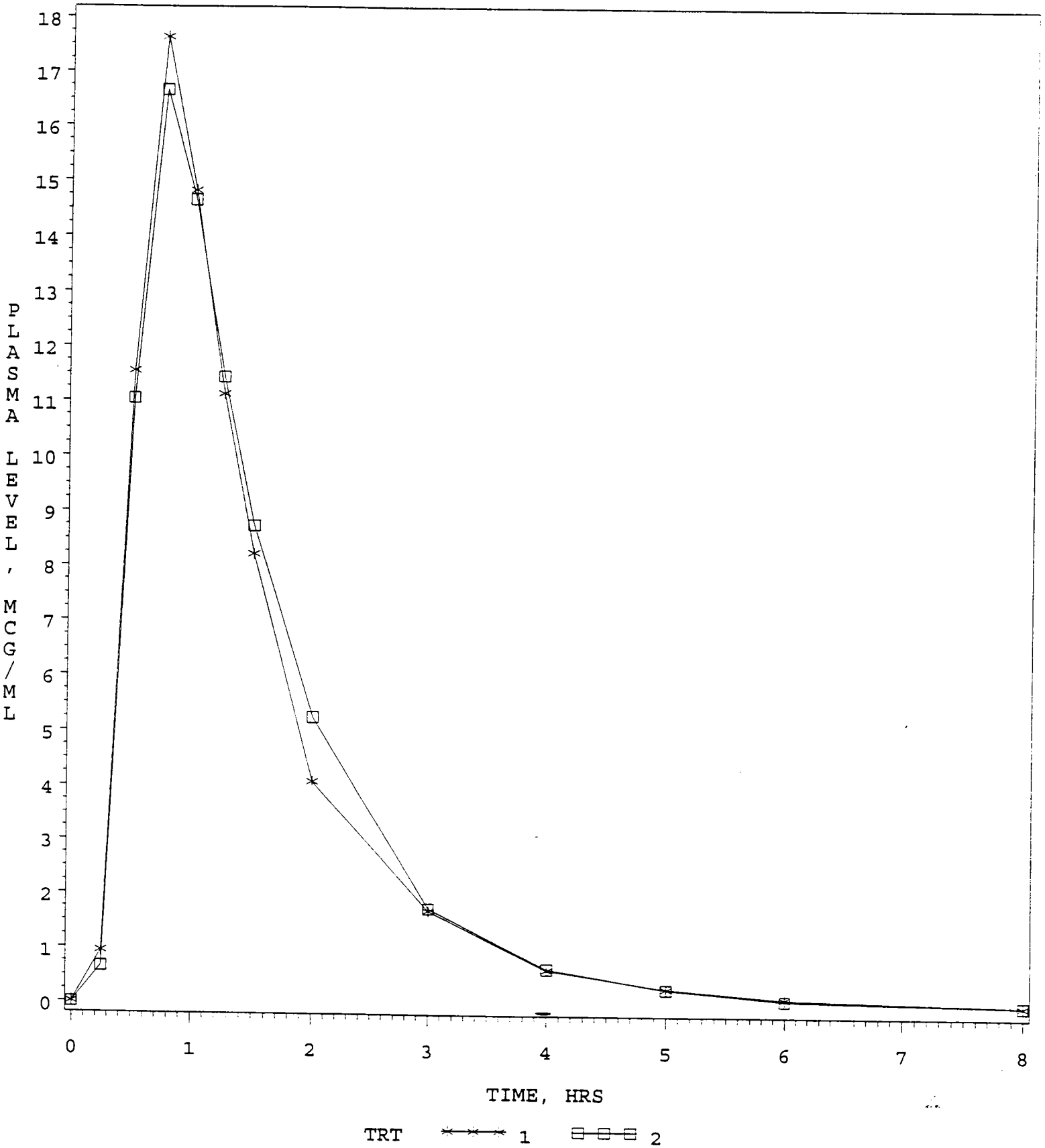
II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #P00194 Strength(mg) 500			Reference Product Lot # 8AA88A Strength(mg)500		
	Mean %	Range	%CV	Mean %	Range	%CV
10	75.52		9.4	81.57		8.7
20	90.05		5.7	87.96		3.8
30	93.83		4.4	91.05		3.2
45	96.3		3.6	95.15		2.8

Sampling Times (Minutes)	Test Product Lot # P00194 Strength(mg) 250			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
10	85.86		3.5			
20	97.14		2.8			
30	100.24		1.8			
45	101.87		1.1			

FIG P-1. PLASMA CEFACLOR LEVELS

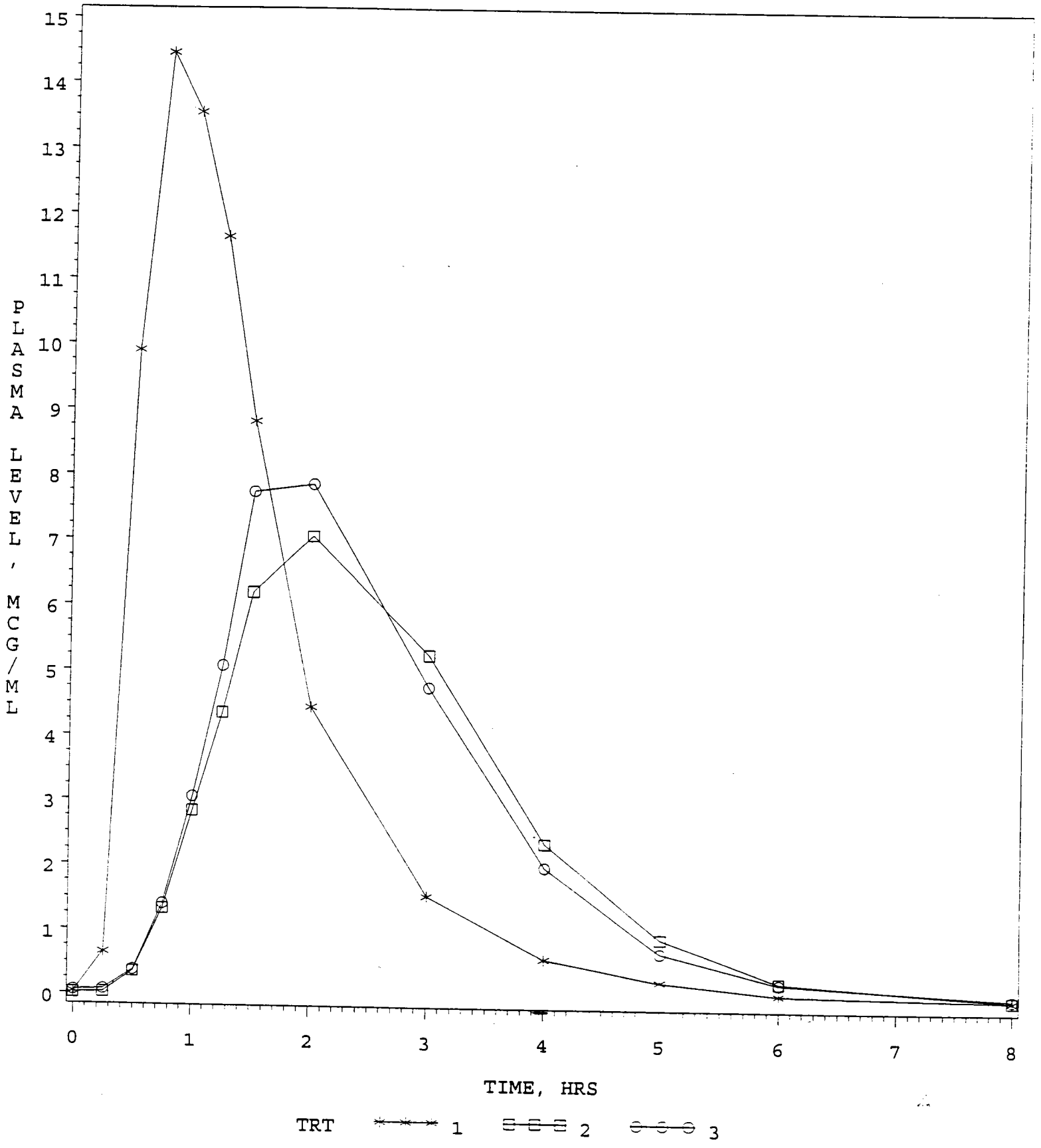
CEFACLOR CAPSULES, 500 MG, ANDA #64-156
UNDER FASTING CONDITIONS
DOSE=500 MG



1=TEST PRODUCT(RANBAXY) 2=REFERENCE PRODUCT(ELI LILLY)

FIG P-2. PLASMA CEFACLOR LEVELS

CEFACLOR CAPSULES, 500 MG, ANDA #64-156
UNDER NON-FASTING CONDITIONS
DOSE=500 MG



1=TEST-FASTING(RANBAXY) 2=TEST-FED(RANBAXY) 3=REFERENCE-FED(ELI LILLY)